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Hyperinsulinemic euglycemic clamp

The gold standard for investigating and quantifying insulin resistance is the "hyperinsulinemic euglycemic clamp," so called because it measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia.[2] The test is rarely performed in clinical care, but is used in medical research - for example, to assess the effects of different medications. The rate of glucose infusion is commonly referred to in diabetes literature as the GINF value.

The procedure takes about 2 hours. Through a peripheral vein, insulin is infused at 10-120 mU per m2 per minute. In order to compensate for the insulin infusion, glucose 20% is infused to maintain blood sugar levels between 5 and 5.5 mmol/l. The rate of glucose infusion is determined by checking the blood sugar levels every 5-10 minutes. Low dose insulin infusions are more useful for assessing the response of the liver whereas high dose insulin infusions are useful for assessing peripheral (i.e. muscle and fat) insulin action.

The rate of glucose infusion during the last 30 minutes of the test determines insulin sensitivity. If high levels (7.5 mg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/min or lower) indicate that the body is resistant to insulin action. Levels between 4.0 and 7.5 mg/min are not definitive and suggest "impaired glucose tolerance," an early sign of insulin resistance.

This basic technique can be significantly enhanced by the use of glucose tracers. Glucose can be labeled with either stable or radioactive atoms. Commonly used tracers are 3-3H glucose (radioactive), 6,6 2H-glucose (stable) and 1-13C Glucose (stable). Prior to beginning the hyperinsulinemic period, a 3h tracer infusion enables one to determine the basal rate of glucose production. During the clamp, the plasma tracer concentrations enable the calculation of whole body insulin stimulated glucose metabolism as well as the production of glucose by the body (i.e. endogenous glucose production).

Modified Insulin Suppression Test

Another measure of insulin resistance is the modified insulin suppression test developed by Gerald Reaven at Stanford University. The test correlates well with the euglycemic clamp with less operator-dependent error. This test has been used to advance the large body of research relating to the metabolic syndrome.

Patients initially receive 25mcg of sandostatin in 5ml of normal saline over 3-5 min IV as an initial bolus and then will be infused continuously with an intravenous infusion of somatostatin (0.27microgm/m2/min) to suppress endogenous insulin and glucose secretion. Insulin and 20% glucose is then infused at rates of 32 and 267mg/m2/min, respectively. Blood glucose is checked at zero, 30, 60, 90 and 120 minutes and then every 10 minutes for the last 1/2 hour of the test. These last 4 values are averaged to determine the steady state plasma glucose level. Subjects with an SSPG greater than 150mg/dl are considered to be insulin resistant.

Alternatives

Given the complicated nature of the "clamp" technique (and the potential dangers of hypoglycemia in some patients), alternatives have been sought to simplify the measurement of insulin resistance. The first was the Homeostatic Model Assessment (HOMA), and a more recent method is the QUICKI (quantitative insulin sensitivity check index). Both employ fasting insulin and glucose levels to calculate

insulin resistance, and both correllate reasonably with the results of clamping studies. Wallace *et al* point out that QUICKI is the logarithm of the value from one of the HOMA equations.[3]